

Acetylation of 3,2'-Nicotyrine

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As part of a research program on utilization of nicotine, a study has been made of the acetylation of 3,2'-nicotyrine (I), which is readily obtained from nicotine by catalytic dehydrogenation³ or oxidation.⁴ The acetylation of N-methylpyrrole⁵ with acetic anhydride and anhydrous sodium acetate has been reported to yield 1-methyl-2-acetylpyrrole. Use of these reagents at

reflux temperature with I, however, gave only a negligible yield of any product. Hartough and Kosak⁶ acetylated thiophene and furan, with iodine and hydriodic acid as catalyst. The efficiency of this catalyst prompted its use in the acetylation of I.

The principal product obtained when (I) is acetylated with acetic anhydride containing small amounts of hydriodic acid and free iodine has been assigned the structure 1-methyl-2-(3-pyridyl)-5-acetylpyrrole (II) on the basis of a comparison of its absorption spectrum with that of the model compound. If anhydrous aluminum chloride is used as catalyst a small yield of an isomeric substance is obtained to which structure (III), 1-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Whitmarsh Research Laboratory, Pennsylvania Salt Mfg. Co., Philadelphia 18, Pa.

(3) (a) Wibaut and Overhoff, *Rec. trav. chim.*, **47**, 935 (1928);

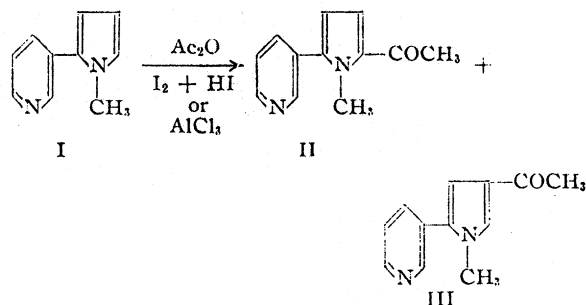
(b) Frank, Holley and Wikholm, *THIS JOURNAL*, **64**, 2835 (1942).

(4) Woodward, Badgett and Haines, U. S. Patent 2,432,642 Dec. 16, 1947).

(5) Ciamician and Deunstedt, *Ser.*, **17**, 2944 (1884).

(6) Hartough and Kosak *THIS JOURNAL*, **68**, 2639 (1946).

methyl-2-(3-pyridyl)-4-acetylpyrrole, has been assigned. As compared with hydriodic acid-iodine or aluminum chloride, bromine, bentonite and silica-alumina catalyst, each in acetic anhydride, were inferior catalysts for the acetylation. The Ehrlich test⁷ applied to each of these two isomeric pyrroles gives an anomalous result in that both isomers are almost negative at room temperature and positive (red color) at steam-bath temperature. This test, normally used to detect pyrroles having an unsubstituted α -position, is unable to differentiate between the acetylnicotyrine isomers.



Comparison of the ultraviolet absorption spectrum of nicotyrine⁸ with that of a phenyl analog, 2-phenyl-4-methylpyrrole (A, Fig. 2), shows close similarity of spectra, the former compound having an absorption maximum at 288 m μ and the latter at 294 m μ . This suggested the possibility of identifying the isomeric acetylnicotyrines by comparison of their spectra with those of analogous phenylacetylpyrroles. As these required phenylacetylpyrroles that had not previously been prepared, it was necessary to develop syntheses for them.

The analog of (II), 2-phenyl-4-methyl-5-acetylpyrrole was prepared, assuming normal directive influences, by the Grignard acetylation of 2-phenyl-4-methylpyrrole; the reaction of α -phenyl- α -aminoacetone hydrochloride with acetylacetone in glacial acetic acid gave 2-phenyl-3-methyl-4-acetyl-5-methylpyrrole, the analog of III. The third compound, 2-phenyl-3-acetyl-5-methylpyrrole was obtained by a Friedel-Crafts acetylation of 2-phenyl-4-carbethoxy-5-methylpyrrole; this yielded 2-phenyl-3-acetyl-4-carbethoxy-5-methylpyrrole, which was then saponified and subsequently thermally decarboxylated.

The ultraviolet spectrum of pyrrole⁹ itself shows no intense maxima but only a steeply rising end absorption as the 200-m μ region is approached. Conjugation of pyrrole with a 3-pyridyl ring as in nicotyrine or nornicotyrine⁸ gives a maximum in the 285 to 295-m μ region for the spectrum in 95% ethanol. When in addition an acetyl group is attached to the pyrrole ring in the 2- or 3-position (compounds II and III; A and D,

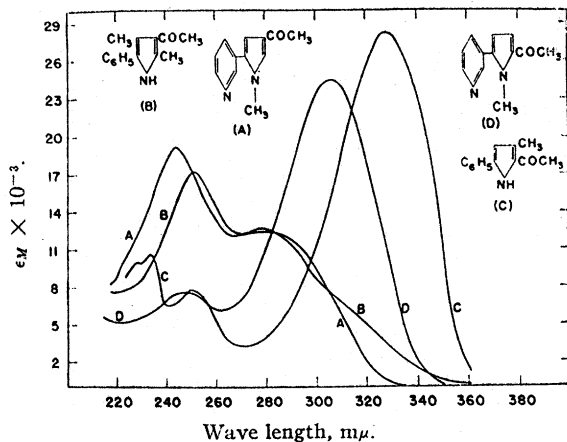


Fig. 1.

Fig. 1), an additional maximum is present in the 240-250-m μ region. As expected, compound II, having a greater extent of conjugation than its isomer, III, absorbs at somewhat longer wave lengths. The spectrum of 2-phenyl-3-acetyl-5-methylpyrrole (B, Fig. 2) is included for comparison.

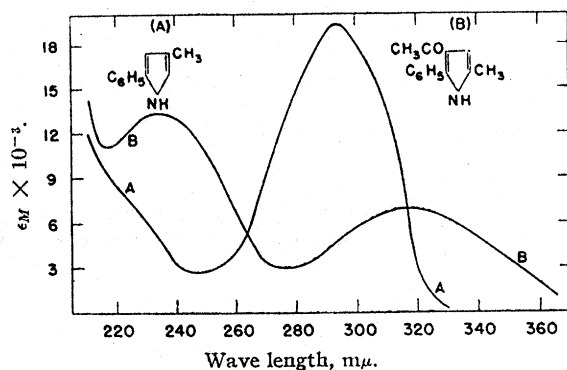


Fig. 2.

The spectral curves of the phenyl analogs in general showed maxima at somewhat longer wave lengths than those of the acetylnicotyrines.

Experimental

Acetylation of 3,2'-Nicotyrine. Method A.—A mixture of 21.0 g. of 3,2'-nicotyrine, 70 ml. of acetic anhydride and 1.3 ml. of 50% aqueous hydriodic acid (containing some free iodine) was refluxed by heating in an oil-bath at 135-140° for seven and one-half hours. While it was cooling in an ice-bath, excess aqueous sodium hydroxide was added gradually with stirring. The alkaline solution was ether extracted, and the extract dried overnight with anhydrous sodium carbonate. The filtered ethereal extract was evaporatively distilled, and the oil residue fractionally distilled. A small forerun of 3,2'-nicotyrine was collected, followed by a 9.1-g. fraction boiling at 151-166° at 0.5 mm. and a 2.3-g. fraction boiling at 171-185° at 0.6 mm. Twelve grams of picric acid was added to the 9.1 g. fraction, and the resulting picrate was recrystallized from water several times. The yield of II picrate (m. p. 197-198°) was 12.6 g. Similar treatment of the highest boiling fraction with 3 g. of picric acid yielded 0.8 g. of picrate melting at 222-223° (III picrate).

(7) Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akad. Verlags., Leipzig, 1934, p. 66.

(8) Swain, Eisner, Woodward and Brice, *THIS JOURNAL*, **71**, 1341 (1949).

(9) (a) Hartley and Dobbie, *J. Chem. Soc.*, 598 (1898); (b) Purvis, *ibid.*, 1048 (1910).

Method B.—Twenty-four grams (0.18 mole) of anhydrous aluminum chloride was added in small portions to an externally cooled solution of 25.0 g. of 3,2'-nicotyrine (0.16 mole) dissolved in a mixture of 50 ml. of acetic anhydride and 50 ml. of glacial acetic acid. The mixture was then refluxed for one and one-half hours. After treatment as in Method A, there were 12.1 g. of crude II (137–155° at 0.7 mm.) and 5.1 g. of crude III (173–185° at 0.7 mm.). These crude products could be further purified as picrates or crystallized from petroleum ether after solidifying overnight in the refrigerator.

Recovery of Bases from Picrates.—The picrate (67.3 g.) of II was treated with enough ice-cold 6 *N* hydrochloric acid to hydrolyze it. The precipitated picric acid was filtered off, and the filtrate cooled in an ice-bath. The cooled solution was made alkaline by the addition of sodium hydroxide at such a rate that the temperature of the solution did not rise above 10°. After extracting with ether, drying the extract with anhydrous sodium carbonate and distilling, there was 29.0 g. of distillate (b. p. 156° at 0.3 mm.) which solidified in the receiver (m. p. 57–58°). Crystallization from petroleum ether (b. p. 35–59°) yielded 25.8 g. of 1-methyl-2-(3-pyridyl)-5-acetylpyrrole (II), m. p. 58–59°.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.59; H, 6.00; N, 14.07.

Addition of a small amount of II to a solution of *p*-dimethylaminobenzaldehyde in hydrochloric acid (Ehrlich test) gave no color at room temperature but a red color when warmed.

A semicarbazone was prepared by the reaction of II with a warm aqueous alcohol solution of semicarbazide hydrochloride after alkalinizing with sodium hydroxide. The II semicarbazone melted at 248–249° after crystallization from 60% ethanol.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 60.68; H, 5.88; N, 27.22. Found: C, 60.62; H, 5.85; N, 27.42.

An oxime was prepared by the reaction of II with a slight excess over an equal molar amount of hydroxylamine hydrochloride in pyridine at steam-bath temperature for one hour, followed by cooling and diluting with water. The II oxime recrystallized from 50% ethanol melted at 174–175°.

Anal. Calcd. for $C_{12}H_{13}N_2O$: C, 66.98; H, 6.05; N, 19.53. Found: C, 67.03; H, 6.07; N, 19.49.

Similar acid hydrolysis of the picrate of III (4.6 g.) yielded 0.9 g. of 1-methyl-2-(3-pyridyl)-4-acetylpyrrole (III). The white crystalline product, m. p. 108–109°, was obtained by crystallization from a 1:1 mixture of benzene and petroleum ether (b. p., 63–70°) containing a small amount of Norit.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.38; H, 6.47; N, 13.73.

The Ehrlich test on III likewise was colorless at room temperature and red on warming.

A semicarbazone of III was prepared in pyridine solution and crystallized from 50% ethanol as cream-colored crystals of m. p. 221–222°.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 60.68; H, 5.88; N, 27.22. Found: C, 60.87; H, 5.86; N, 27.38.

2-Phenyl-4-methylpyrrole.—This compound was prepared by a modification of the method of Piloty and Hirsch,¹⁰ with substitution of an acid medium for the original lengthy reaction in alkaline solution.

A mixture of 75 ml. of glacial acetic acid, 6 g. of acetophenone and 8 ml. of an aqueous solution containing about 4 g. of amino-acetone hydrochloride¹¹ was refluxed for three hours. The mixture was diluted with several liters of water, made strongly alkaline with sodium hydroxide, and then distilled. After the first 250 ml. of distillate (water and acetophenone) was discarded, the pyrrole was obtained as white crystals (0.4 g.) separating from the remainder of the distillate. Crystallization from 25%

ethanol gave 0.3 g. of white crystals, m. p. 150–152°, which rapidly discolored on standing.

2-Phenyl-4-methyl-5-acetylpyrrole.—In an atmosphere of dry nitrogen, a mixture of 100 ml. of anhydrous ethyl ether, 0.19 g. of magnesium turnings (0.008 g. atom) and 0.9 g. of ethyl bromide (0.008 mole) was refluxed until all the magnesium had reacted. The open end of the condenser was protected by a calcium chloride tube. A solution of 1.1 g. of 2-phenyl-4-methylpyrrole (0.007 mole) in 25 ml. of anhydrous ether was gradually added through a dropping funnel. After it had been refluxed for about fifteen minutes, a solution of 0.55 g. of acetyl chloride (0.007 mole) in 10 ml. of anhydrous ether was added, and gentle refluxing was continued for one-half hour more. One hundred ml. of aqueous ammonium chloride solution was added, and the ether layer was separated, filtered, and then evaporated to dryness. Crystallization of the residue from petroleum ether (b. p. 95–127°) yielded 0.4 g. of pink crystals melting at 159–160°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 78.43; H, 6.63; N, 6.80.

2-Phenyl-3,5-dimethyl-4-acetylpyrrole.—A mixture of 3.0 g. of α -amino- α -phenylacetone hydrochloride¹² (0.016 mole), 1.8 g. of acetylacetone (0.018 mole) and 35 ml. of glacial acetic acid was refluxed for one hour. After cooling the product was filtered off. It was crystallized once from 50% acetic acid and then several times from 25% ethanol, yielding 0.5 g. of cream-colored crystals, m. p. 158–159°. The Ehrlich test was negative at room temperature and positive at boiling temperature.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.87; H, 7.04; N, 6.57. Found: C, 78.41; H, 7.58; N, 6.60.

2-Methyl-3-carbethoxy-5-phenylpyrrole.—Attempts to prepare this compound by the reaction of phenacylacetate with aqueous ammonia as described by Lederer and Paal¹³ yielded only resin. However, reaction with ammonium acetate in acetic acid gave the desired product.

Forty grams of ammonium carbonate was gradually added to a solution of 10 g. of phenacylacetate in a mixture of 110 ml. of glacial acetic acid and 10 ml. of water. The resulting reaction mixture was heated on the steam-bath for one hour. Thirty-five ml. of water was gradually added while cooling and stirring the mixture. The precipitate which formed on standing overnight was collected and briefly air dried on the filter. The product was dissolved in benzene, and the solution was filtered. The addition of petroleum ether (b. p., 63–70°) to the benzene solution precipitated the pyrrole. Crystallization from benzene-petroleum ether (b. p., 63–70°) mixture (1:2 by vol.) yielded 5.3 g. of white crystals of m. p. 114–115° (lit.¹³ 120°). The Ehrlich test was positive at room temperature.

2-Phenyl-3-acetyl-4-carbethoxy-5-methylpyrrole.—In a flask previously swept out with dry nitrogen gas was placed 5.0 g. of 2-methyl-3-carbethoxy-5-phenylpyrrole (0.022 mole), 40 ml. of anhydrous carbon disulfide, 1.7 g. of acetyl chloride (0.022 mole), and 2.9 g. of anhydrous aluminum chloride (0.022 mole). The open end of the reflux condenser was fitted with a calcium chloride drying tube, and the mixture was refluxed for one hour. An orange-yellow precipitate formed immediately on addition of the aluminum chloride, which was added last. After the solvent was distilled off, water was added, and the pasty mass gradually crystallized. The material on the filter was washed with copious amounts of water before crystallizing from aqueous alcohol and from benzene-petroleum ether (b. p., 95–127°) mixture (2:3). The yield was 4.5 g. of crystals which melted at 80–124°. As this appeared to be a mixture of product and starting material, it was recycled with fresh acetylating agent. This raised the melting point, but still another recycling was necessary to obtain a pure product. The final yield was 1.9 g. of cream-colored crystals which melted at 138–

(10) Piloty and Hirsch, *Ann.*, **395**, 93 (1913).

(11) Neber and Huh, *ibid.*, **515**, 283 (1935).

(12) Neber and Friedolsheim, *ibid.*, **449**, 109 (1926).

(13) Lederer and Paal, *Ber.*, **18**, 2591 (1885).

(14) Paal, *ibid.*, **16**, 2865 (1883).

140°. The Ehrlich test was negative at room temperature and positive at steam-bath temperature, indicating that the acetyl group was attached to the pyrrole ring rather than phenyl.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 70.85; H, 6.27; N, 5.17. Found: C, 71.18; H, 6.50; N, 4.99.

2-Phenyl-3-acetyl-5-methylpyrrole.—The pyrrolecarboxylic acid ester (1.5 g.) was refluxed for four hours in a solution of 1.0 g. of sodium hydroxide in 150 ml. of 50% ethanol. The product presumed to be 2-phenyl-3-acetyl-5-methyl-4-pyrrolecarboxylic acid, was precipitated by gradual addition of a mixture of 4 ml. of concentrated hydrochloric acid in 96 ml. of water. Crystallization from 50% ethanol yielded 0.6 g. of cream-colored crystals which melted at 249–251° (uncor.) with evolution of gas.

The acid was decarboxylated by heating in a test-tube immersed in an oil-bath maintained at 250–255° until gas evolution ceased. After being cooled, the dark-brown mass was crystallized from petroleum ether (b. p., 95–127°) containing a little benzene and Norit. The yield was 0.2 g. of white crystals which melted at 142–143°. The Ehrlich test at room temperature was negative at the beginning and became weakly positive after standing for several hours. At steam-bath temperature, the test was immediately positive.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 78.12; H, 6.82; N, 6.85.

Ultraviolet Absorption Spectra.—The spectra were obtained with a Beckman Model DU spectrophotometer. The solvent was 95% ethanol, used without further purification. The spectrum of 2-phenyl-4-methylpyrrole is included for purposes of comparison.

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Summary

Acetylation of 3,2'-nicotyrine has produced a mixture of two isomers which can be separated by fractional distillation. They have been assigned the structures of 1-methyl-2-(3-pyridyl)-5-acetylpyrrole and 1-methyl-2-(3-pyridyl)-4-acetylpyrrole.

Structures were assigned to the two products by comparison of their ultraviolet absorption spectra with those of 2-phenyl-4-methyl-5-acetylpyrrole, 2-phenyl-3,5-dimethyl-4-acetylpyrrole and 2-phenyl-3-acetyl-5-methylpyrrole. The syntheses of these new pyrrole derivatives are described.